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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,725	12/21/2001	Sabine Flicker	25401-4	9787

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,725	FLICKER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *26-33,35-38,40-43,45 and 46* is/are allowed.

6)☒ Claim(s) *34 and 44* is/are rejected.

7)☒ Claim(s) *25 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 25-46 are pending.

2. In view of the amendment filed 1/23/06, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 34 and 44 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a timothy grass Phl p2 pollen allergen specific human IgE Fab for detection assay and for standardization of allergen extract using timothy grass Phl p2 pollen specific antibody comprising a heavy chain consisting of the amino acid sequence as shown in SEQ ID NO: 7, SEQ ID NO: 8 or SEQ ID NO: 9, and a light chain consisting of the amino acid sequence as shown in SEQ I DNO: 10, SEQ ID NO: 11 or SEQ ID NO: 12, respectively, **does not** reasonably provide enablement for (1) any vaccine against any type I allergy comprising the any group 2 allergen specific human IgE Fab having a heavy chain consisting of an amino acid sequence as shown in SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID NO: 9 and a light chain consisting of an amino acid sequence as shown in SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 12, respectively, and (2) any vaccine against any type I allergen as set forth in claim 44. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The breath of the claims encompasses any a vaccine against any type I allergy using the human IgE Fab fragment and the corresponding complete antibody or the human IgE Fab fragment having the amino acid sequence of SEQ ID NO: 7-12 encoded by nucleic acid sequence of SEQ ID NO: 1-6 or the corresponding complete antibody.

The specification discloses only three timothy grass pollen Phl p2 allergen specific human IgE Fab fragments consisting of a heavy chain *and* a light chain wherein the heavy chain amino acid sequence consists of SEQ ID NO: 7 and the light chain amino acid sequence consists of SEQ ID NO: 10 or a heavy chain consisting of SEQ ID NO: 8 and a light chain consisting of SEQ ID NO: 11, or a heavy chain consisting of SEQ ID NO: 9 and a light chain consisting of SEQ ID NO: 12 for inhibiting the binding of grass pollen allergic patient's IgE to Phl 2 in vitro, (2) An Phlp2 specific antibody comprising the variable region comprising a heavy chain, *and* a light chain of a human IgG1 wherein the variable region comprises a heavy chain amino acid sequence is set forth in SEQ ID NO: 7 and the light chain amino acid sequence is set forth in SEQ ID NO: 10 or a heavy chain is set forth in SEQ ID NO: 8 and a light chain is set forth in SEQ ID NO: 11, or a heavy chain is set forth in SEQ ID NO: 9 and a light chain is set forth in SEQ ID NO: 12 for inhibiting the binding of grass pollen allergic patient's IgE to Phl 2 in vitro, and (3) a diagnostic reagent or a kit comprising said Phl p2 specific human IgE Fabs and/or said specific Phl p2 antibody mentioned above for detection assay (See pages 13 and 17-18). The specification further discloses all three IgE Fabs bound to the same recombinant fragment consisting of the N-terminal 64 amino acids of Phl p2. The specification discloses grafting the variable regions of the Phl p2 specific human IgE Fab fragments onto human IgG1 (page 3) for suppressing Phl p2 degranulation of basophiles. The specification discloses the claimed the recombinant phl p2-specific IgE Fabs may be useful for induction of a protective mucosal immunity (see page 16).

The specification does not teach any vaccine using the claimed phl p2- specific IgE Fab or the corresponding complete antibody, any antibody comprising any combination of heavy and light chain, and any combination of IgE Fab and complete antibody. The intended use of a "vaccine" is for *preventive* purpose. There is a lack of in vivo working example demonstrating that the claimed Fab antibody or the whole corresponding Ig is effective as a vaccine to prevent grass pollen group 2 allergy. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to

the very narrowly defined and controlled conditions for an in vitro assay does not permit a single extrapolation of vitro assays to human prevention of type I allergy with any reasonable degree of predictability.

Freshney et al, of record, teach culture environment lacks the several systemic components involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro than in vivo, but may not be truly representative of the tissue fro which the cells were derived (see enclosed pages in Culture of Animal Cells, in particular).

Denepoux et al, of record, teach various recombinant human monoclonal antibody Fabs to birch pollen allergen Bet v1 such as rBAB2 cannot interfere with allergic effector cells, mast cells, and basophils because they lack Fc region. However, this antibody whose binding to its allergen further enhances the binding of anaphylactic IgE and thus contributes to disease aggravation rather than reduce allergen-induced allergic reaction (see page 46, col. 1, abstract, in particular).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/23/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 34 and 44 are directed to vaccines comprising the IgE Fab according to claim 45 and claim 46, respective, or the corresponding complete antibody. As these claims are recite vaccine compositions, they are fully enabled by the present specification, without reciting any intended use thereof. The specification at page 1 discloses Phl p2 is defined as grass pollen specific IgE-Fabs. The specification at pages 5-16 therapeutic potential, for example building of the stable defense line against intruding allergens and/or inducing a protective mucosal immunity.

In response, the specification at page 16 disclose the recombinant Phl p2 specific IgE Fabs may be useful for preventive measures. A vaccine in the absence of in vivo working example are unpredictable for the following reasons: (1) the Fabs may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the Fabs; (2) the Fabs may not reach the target area because, i.e. the Fabs may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the Fabs unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Further, the specification does not adequately teach how to effectively "prevent" any allergy associated with grass pollen group 2 in humans by administering Fabs. The specification does not teach how to predict who would have allergy to grass pollen group 2 allergen. The specification does not teach how to extrapolate data obtained from in vitro binding inhibition assays to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention.

As evidence by the teachings of Denepoux et al, Denepoux et al teach various recombinant human monoclonal antibody Fabs to birch pollen allergen Bet v1 such as rBAB2 cannot interfere with allergic effector cells, mast cells, and basophils because they lack Fc region. However, this antibody whose binding to its allergen further enhances the binding of anaphylactic IgE and thus contributes to disease aggravation rather than reduce allergen-induced allergic reaction (see page 46, col. 1, abstract, in particular). Therefore, it is not clear that the skilled artisan could predict the efficacy of the grass pollen group 2 allergen specific human IgE Fab exemplified in the specification for preventing allergy encompassed by the claims. Note, a composition comprising the IgE Fab according to claim 45 or the corresponding complete antibody for treating grass pollen group 2 allergy would obviate this rejection.

5. Claims 25 and 39 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 45 and 46, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). It is suggested that claims 25 and 39 be deleted.

6. Claims 26-33, 35-38, 40-43, and 45-46 are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

9. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 14, 2006

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